The Use of Copper as an Antimicrobial Agent in Health Care, Including Obstetrics and Gynecology

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SUMMARY Health care-associated infections (HAIs) are a global problem associated with significant morbidity and mortality. Controlling the spread of antimicrobial-resistant bacteria is a major public health challenge, and antimicrobial resistance has become one of the most important global problems in current times. The antimicrobial effect of copper has been known for centuries, and ongoing research is being conducted on the use of copper-coated hard and soft surfaces for reduction of microbial contamination and, subsequently, reduction of HAIs. This review provides an overview of the historical and current evidence of the antimicrobial and wound-healing properties of copper and explores its possible utility in obstetrics and gynecology.

KEYWORDS health care-associated infections, antibiotic resistance, antimicrobial activity, antimicrobial agents, copper, gynecology, microorganisms, obstetrics, wound healing

INTRODUCTION

Health care-associated infections (HAIs) are a global problem associated with significant morbidity and mortality. With an overall prevalence rate of 7.1%, over 4.1 million patients are affected in Europe (1). In the emergency department, more than half of the patients suffer from an HAI, leading to 16 million extra days of hospitaliza-

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tion, with a cost estimate of approximately 7 billion euros (1). In Europe, 37,000 deaths can be attributed directly to HAIs, and in an additional 110,000 deaths, HAI is a contributory factor (1). The management of HAIs with antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) is becoming increasingly problematic (2). Although the prevalence of MRSA in Europe is decreasing, an incidence rate of up to 65% of all isolates in 2013 has been reported (3). The most concerning trends in Europe over recent years were related to the occurrence of antibiotic-resistant Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* species). The incidence of antimicrobial-resistant isolates is currently one of the most important benchmarks of global health care. Attempts to reduce the distribution of antimicrobial-resistant pathogens have become a major priority of health services. In the United Kingdom, antibiotic consumption during 2011 to 2014 (4) increased by 6.5%, and in the United States, 68% of the courses of antibiotics were inappropriately prescribed (5). Even more concerning is that it has been 30 years since the last antibiotic agent has been developed, and only 3 out of the 41 newly developing antibiotics are sensitive against the majority of resistant bacteria (6). Developing a new generation of antibiotics is going to be a challenge and would provide only a temporary option before resistance develops. Furthermore, these antibiotics may not be easily available in low-resource countries. It is therefore crucial that investment is made into research to identify other antimicrobial agents that can prevent and treat hospital-acquired infections.

Recent research in microbiology has begun to focus on copper. The biocidal effect of copper on a wide range of pathogens, such as bacteria, fungi, and viruses, has been demonstrated by many laboratory studies (7, 8). The effectiveness of copper extends to MRSA (9) and VRE (1). Apart from being an effective antimicrobial agent, exposure to copper has been correlated with enhanced wound healing (10). The substitution of copper alloys on surfaces within a clinical setting has been demonstrated to significantly reduce bacterial colonization (11, 12), and more recently, copper-infused fabrics have also been studied (13).

In the field of obstetrics and gynecology, infection prevention practices are challenging. The "normal" microflora of the vagina and cervix can, under certain circumstances, lead to infection of the female genital tract, and these infections are usually caused by more than one microbe, both aerobic and anaerobic (14, 15). From a global perspective, maternal sepsis is the third major cause of death, representing about 11% of all maternal deaths (16). Sepsis is the leading direct cause of maternal mortality in the United Kingdom (17).

In this review, our aim is primarily to explore the current available evidence with regard to the antimicrobial effects of copper-based materials. Given the high morbidity and mortality associated with maternal sepsis (16), we also evaluate the potential benefits and clinical applications of copper within obstetrics and gynecology.

HISTORICAL PERSPECTIVE

The Egyptians were the first to mention the antimicrobial effects of copper in 2600 BC. They used copper vessels to sanitize drinking water and also to treat chest wounds. In papyrus circa 1500 BC, it was stated that various adaptations of copper were used to treat infections, scalds, and itching (18). In Cyprus, a Greek island, copper was found in large quantities, and therefore, it was used frequently by the ancient Greeks. This is also the basis from which the Latin name for copper, cuprus, was derived. In the Hippocratic Collection, which was partially written by the great Greek physician Hippocrates (460 to 377 BC), it was stated that copper-containing wound dressings were recommended to treat leg ulcers, and infection of fresh wounds was prevented by sprinkling dry copper powder on the wound. In another important first-century medical writing, De Medicina, written by the Roman Aulus Cornelius Celsus, copper is mentioned as an important drug for practicing physicians, namely, to treat venereal diseases and nonhealing chronic ulcers. During the two great European cholera epidemics in the 19th century, copper suppressed a cholera outbreak among workers in the copper industry (19).

Despite the demonstrated benefits, interest in copper diminished due to the limited understanding of the mechanisms of antimicrobial action and basis of promotion of wound healing, but more importantly, it was superseded by the discovery of antibiotics.

IN VITRO ANTIMICROBIAL ACTIVITY OF COPPER

Considerable research has been conducted globally to establish the antimicrobial spectrum of copper. Copper been demonstrated not only to inhibit growth but also to effectively eradicate microorganisms, including those causing HAIs.

Bacteria

In 1975, Majno was the first to reproduce and experimentally demonstrate the antibacterial abilities of ancient copper compounds (20). Recreating the copper compounds mentioned in the Smith Papyrus, he ground malachite and chrysocolla to a fine powder and made verdigris, using the oldest method known, by converting copper to vapor from vinegar. He then inoculated the three different compounds with three bacteria isolated from a wound and discovered that no bacteria grew in the proximity of the three compounds, thereby providing evidence of their antiseptic abilities. In the 1990s, Bill Keevil and his team conducted considerable research at the University of Southampton, United Kingdom. His interest was piqued when he observed lower levels of contamination with *Legionella* on plumbing systems made with copper than on those made with stainless steel or plastic (21). Through a series of laboratory tests, including a broad spectrum of microbes and testing under different conditions (temperature and humidity), he confirmed the antimicrobial ability of copper and copper alloys (22–25). His team tested the survival of high concentrations of *Escherichia coli* O157 bacteria on different metal surfaces such as stainless steel, copper, and copper alloys and showed survival for more than 28 days on stainless steel. In contrast, no bacteria were found after 90 to 270 min at 20°C and 4°C, respectively, on a copper surface. Copper alloys also demonstrated the antibacterial ability, whereby the effect increased with increasing copper concentrations (22). They continued their research by looking at the survival time of *Listeria monocytogenes* on 25 different metal alloys and found a great reduction of survival times on copper-based alloys compared to stainless steel. On stainless steel, viable bacteria could still be retrieved after 24 h, whereas on copper alloys, no viable bacteria could be retrieved after 60 min (23).

Copper has also been shown to be effective against antibiotic-resistant bacteria such as MRSA (9, 26) or VRE (27). The first study was published in 2006 whereby copper and stainless steel coupons were inoculated with three MRSA strains (MRSA, EMRSA-1, and EMRSA-16) and incubated at 22°C and 4°C. The results demonstrated a complete kill of MRSA in 45 to 90 min on pure copper at room temperature. A complete kill was achieved within 6 h for all three strains at 4°C. In contrast, MRSA was still viable after 72 h on stainless steel (9).

An independent laboratory in the United Kingdom has done several *in vitro* tests comparing the antibacterial abilities of several bioactive wound dressings (Fig. 1 to 3). The different wound dressing coupons were inoculated with approximately 10^5 to 10^6 CFU of *S. aureus*, *K. pneumoniae*, and MRSA and incubated for 24 h at 24°C at >95% humidity. Their results showed a significant >1-log reduction of *S. aureus* on two of the four silver dressings, and there was no significant reduction with the other two silver dressings. A significant reduction of *K. pneumoniae* was observed on all four silver dressings, ranging between a 2-log and a >4-log reduction. On the alginate-honey dressing, a significant >1-log reduction was observed for both bacteria. On the 3% copper–zinc dressing, a >4-log reduction of both *S. aureus* and *K. pneumoniae* was observed. Dressings with two different copper concentrations (2% and 3%) were also tested against MRSA, which showed a greater reduction of MRSA with increased copper concentrations (Fig. 3). In summary, copper-impregnated dressings showed a greater reduction of *S. aureus* and a similar reduction of *K. pneumoniae*. The alginate-honey dressing showed a similar reduction of *S. aureus* compared to the silver dressings and a lower reduction of *K. pneumoniae* than the silver and copper dressings. A higher
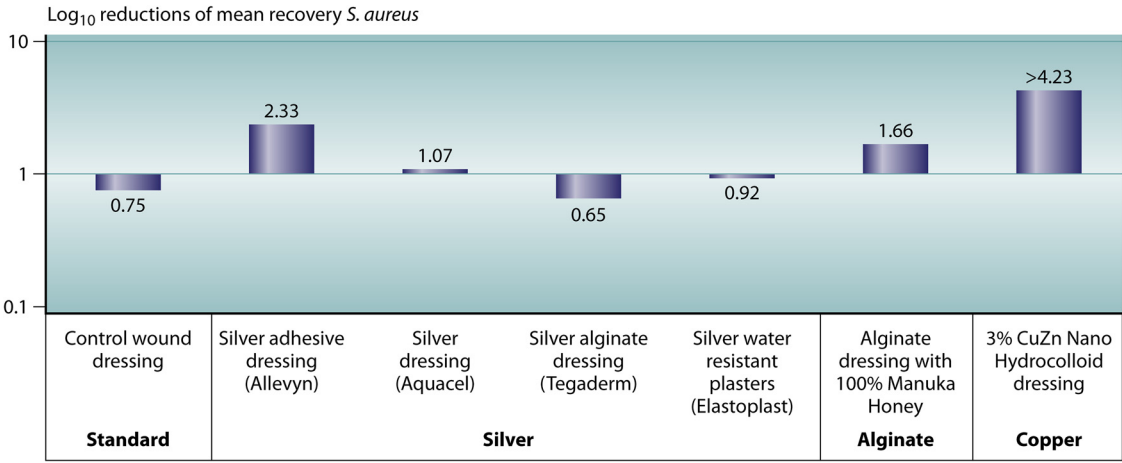
Log$_{10}$ reductions of mean recovery *S. aureus*

FIG 1 Antibacterial activities of different wound dressings against *S. aureus*. *Staphylococcus aureus* was prepared to approximately 10^6 CFU/ml in 0.85% NaCl. For each sample of wound dressing, five replicate test pieces were inoculated on the wound-facing surface with an appropriate volume of *S. aureus*. The inoculates were held for 24 h at 24°C $\pm$ 1°C at >95% humidity. A significant log reduction in the numbers of *S. aureus* bacteria was observed for two of the four silver dressings, the alginate-honey dressing, and the 3% CuZn dressing, with the highest log reduction observed for the copper dressing.

copper concentration resulted in a greater log reduction of MRSA. Borkow et al. conducted *in vitro* and animal studies on a copper oxide-impregnated wound dressing (28). The *in vitro* studies demonstrated potent broad-spectrum antibacterial and antifungal activities of the wound dressings, with a reduction of the bacterial burden associated with the tissues of >99.9%. Tests comparing copper oxide-impregnated dressings to those impregnated with silver leachates found that the copper dressings were superior in providing a significantly greater reduction of the bacterial load.

See Table 1 for a complete overview of the antimicrobial spectrum of copper.

Viruses

As early as 1958, experiments demonstrated the possible antiviral abilities of copper and copper compounds (29). In 2007, Keevil's team demonstrated the effectiveness of copper against influenza A virus (24). They inoculated coupons of either copper or stainless steel with 2×10^6 virus particles and incubated the coupons at room temperature for 1 to 24 h. After 24 h, 5×10^5 infectious virus particles were observed, in contrast to 5×10^2 infectious virus particles on copper (24). In a similar study, they looked at the survival of norovirus on stainless steel and compared it to that on copper alloys; they demonstrated a significant reduction of active norovirus after 2 h on copper alloys. Furthermore, they found that inactivation of the virus was dependent on

Log$_{10}$ reductions of mean recovery *K. pneumoniae*
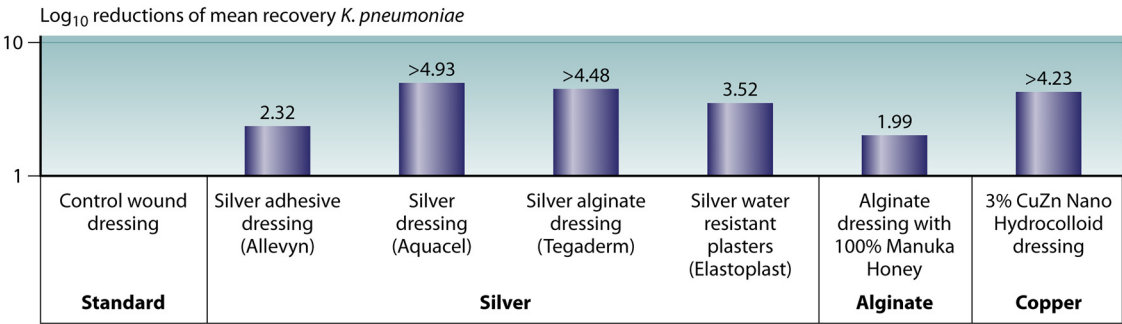
FIG 2 Antibacterial activities of different wound dressings against *K. pneumoniae*. *Klebsiella pneumoniae* was prepared to approximately 10^6 CFU/ml in 0.85% NaCl. For each sample of wound dressing, five replicate test pieces were inoculated on the wound-facing surface with an appropriate volume of *K. pneumoniae*. The inoculates were held for 24 h at 24°C $\pm$ 1°C at >95% humidity. A significant log reduction in the numbers of *K. pneumoniae* bacteria was observed for all the silver dressings, the alginate-honey dressing, and the 3% CuZn dressing.

Log$_{10}$ reductions of mean recovery MRSA

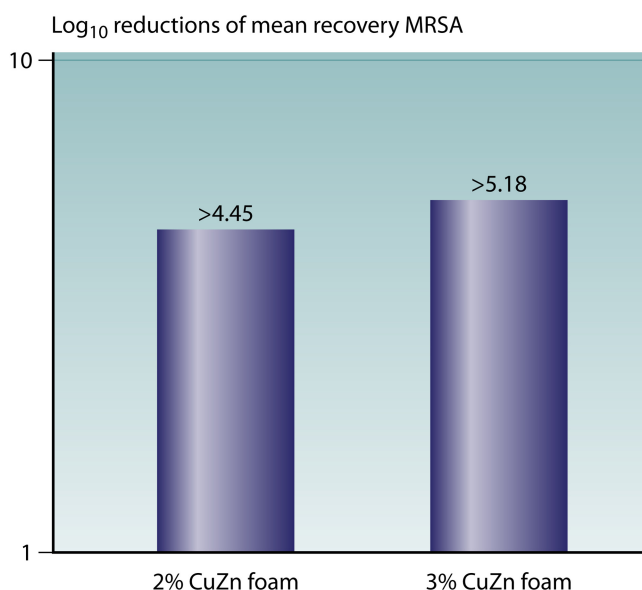FIG 3 Antibacterial activities of two wound dressings with different copper concentrations against MRSA. Methicillin-resistant *Staphylococcus aureus* (MRSA) (NC 11939-09) was prepared to approximately 10^6 CFU/ml in 0.85% NaCl. For each sample of wound dressing, five replicate test pieces were inoculated on the wound-facing surface with an appropriate volume of MRSA. The inoculates were held for 24 h at 24°C ± 1°C at >95% humidity. A significant log reduction was observed for both copper dressings, and an increased log reduction was observed with an increased copper concentration.

humidity and temperature; there was a lower rate of inactivation when the inoculum was suspended in a larger volume, such that evaporation was slower at the lower temperature (30).

See Table 1 for a complete overview of the antiviral spectrum of copper.

Fungi

In contrast to the antibacterial effect, the antifungal ability of copper has not been studied extensively. Weaver et al. studied the effectiveness of copper against various fungi (*Aspergillus* spp., *Fusarium* spp., *Penicillium chrysogenum*, and *Candida albicans*) (31). Copper coupons were inoculated with 20 μl of a suspension of fungal spores for exposure times varying from 0 to 576 h at room temperature and humidity. Surviving spores were visualized using the fluorochrome FUN-1. They found that copper was able to kill all the fungi except *Aspergillus niger*. Moreover, copper was able to prevent the germination of fungal spores. The mechanism by which fungi are killed on copper was found to be similar to the mechanism by which bacteria are killed. Quaranta et al. found that the antifungal effect starts with extensive fungal membrane damage, which was followed by enlargement and disappearance of vacuoles and oxidative stress (32).

See Table 1 for a complete overview of the antifungal spectrum of copper.

Effect of Copper Surfaces

Copper and copper alloys have been studied in experiments simulating a clinical setting by using moist and dry inoculation techniques (33). Many *in vitro* studies have demonstrated the antimicrobial effect of copper on a wide spectrum of Gram-positive bacteria (i.e., *Enterococcus* spp. and *Staphylococcus* spp.), Gram-negative bacteria (i.e., *Acinetobacter* spp., *Campylobacter jejuni*, *E. coli*, and *Pseudomonas* spp.), viruses (i.e., influenza A virus, herpes simplex virus, and human immunodeficiency virus [HIV]), and fungi and yeasts (i.e., *Candida* spp.) (Table 1). The biocidal efficacy is dependent on the copper concentration, length of exposure, humidity, and temperature. Various studies have experimented with the copper concentration (9, 22, 24, 25, 32, 34–38) and different lengths of exposure (9, 22, 23, 39) to achieve the most efficient biocidal effect,

TABLE 1 Antimicrobial efficacy of copper

Organism	Reference(s)
Bacteria	
Gram positive	
Bacillus spp.	38, 112, 256–269
Brachybacterium conglomeratum	270
Clostridium difficile	25, 101, 271, 272
Clostridium tyrobutyricum	273
Deinococcus radiodurans	38
Enterococcus spp.[a]	12, 13, 28, 36, 45, 46, 55, 83, 101, 103, 104, 107, 258, 271, 274–280
Kocuria spp.	270
Listeria monocytogenes	23, 55, 274, 281, 282
Micrococcus luteus	45, 46, 260, 270
Mycobacterium tuberculosis[a]	35
Sarcina lutea	256
Staphylococcus spp.[a]	9, 12, 13, 26, 28, 35, 44–46, 55–57, 68, 101, 103, 104, 107, 112, 250, 251, 256–259, 262, 263, 266–268, 270, 271, 275, 276, 281–298
Streptococcus spp.	107, 257–260, 297, 299
Gram negative	
Acinetobacter spp.[a]	35, 112, 171, 257, 270, 271, 275, 276, 285, 300, 301
Campylobacter jejuni	173
Citrobacter freundii	257, 302
Cronobacter sakazakii	42, 344
Desulfovibrio desulfuricans	303
Edwardsiella tarda	304
Enterobacter spp.[a]	45, 46, 112, 258, 259, 274, 276, 286, 301
Escherichia coli[a]	13, 22, 28, 34, 38, 40, 41, 45, 46, 55–57, 64, 65, 83, 112, 257, 258, 260–263, 266–268, 270, 276, 278, 286–290, 297, 301, 305–313
Klebsiella pneumoniae[a]	28, 35, 112, 257, 260, 275, 276, 284, 287, 301, 305, 306, 314
Legionella pneumophila	23, 271, 315–318
Methylobacterium spp.	261
Morganella morganii	302
Pantoea stewartii	270
Photobacterium leiognathi	28
Proteus spp.	258, 314
Pseudomonas spp.[a]	28, 35, 45, 46, 112, 171, 256, 258–260, 262, 263, 267, 269, 270, 275, 276, 281, 286, 301, 314, 319–321
Salmonella spp.[a]	43, 55, 64, 173, 257, 268, 281, 302, 307, 309, 314, 319, 321–324
Serratia marcescens	267
Shewanella putrefaciens	281
Shigella spp.	257, 268, 302, 314, 322
Sphingomonas panni	270
Sphingomonas sp.	261
Stenotrophomonas maltophilia	171
Vibrio cholerae[a]	307, 323, 325
Xanthomonas campestris	326
Yersinia pseudotuberculosis	274
Viruses	
Enveloped	
Avian influenza virus	61, 283
Bacteriophages	327–331
Cytomegalovirus	332
Herpes simplex virus	327, 328
Human immunodeficiency virus	13, 332–334
Infectious bronchitis virus	335
Influenza A virus	24, 61, 332, 336
Junin virus	328
Measles virus	332
Parainfluenza virus 3	332
Pichinde virus	332

(Continued on next page)

TABLE 1 (Continued)

Organism	Reference(s)
Punta Toro virus	332
Respiratory syncytial virus	332
Vaccinia virus	332
West Nile virus	13
Yellow fever virus	332
Nonenveloped	
Adenovirus type 1	332
Bacteriophages	327–331
Murine norovirus	30
Poliovirus	331, 337
Rhinovirus 2	332
Fungi/yeast	
Alternaria brassicae	326
Aspergillus spp.	31, 260, 262, 319, 322, 326, 338–342
Candida spp.	13, 28, 31, 32, 35, 55, 56, 108, 112, 258, 260, 263, 264, 274–276, 305, 314, 322, 338, 340, 342, 343
Cryptococcus neoformans	340
Curvularia lunata	284
Epidermophyton floccosum	340
Fusarium spp.	31, 284, 322, 326
Microsporum canis	322, 340
Myrothecium verrucaria	341
Penicillium chrysogenum	31
Pleurotus ostreatus	308
Pycnoporus cinnabarinus	308
Rhizoctonia spp.	284, 319
Saccharomyces cerevisiae	32, 62, 263, 345
Torulopsis pintolopesii	343
Trichoderma viride	341
Trichophyton spp.	314, 322, 338, 340, 341

[a]Including antibiotic-resistant strains.

with the majority of the research having been conducted by the research team of Keevil in Southampton, United Kingdom (9, 22, 24–26, 30, 34, 36). They placed a higher concentration of bacteria (40) onto coupons with different concentrations of copper ranging between 0% (100% stainless steel or 100% metallic zinc) and 100% but varying the time of surface exposure of the microbes to the metal from several minutes to up to 24 h. Viable microbes were counted after staining for visualization by epifluorescence microscopy. They demonstrated that the biocidal efficacy increases with higher copper concentrations. A significant biocidal effect was reached using metals with a copper concentration of between 55% and 100%; there was a complete eradication of microbes within 90 min on pure copper and 120 min on copper nickel with a 75% copper concentration (22). Copper continuously reduced microbial contamination, with a 99.9% reduction within 2 h of exposure. Initial studies were done using a wet inoculum at high relative humidity (>90%) and incubated at high temperatures (35°C). However, as this would not reflect a clinical setting, different laboratory techniques have been used. One difference is the use of either a dry inoculum (reflecting touch contamination) or a wet inoculum (reflecting wet contamination such as a sneeze). It was found that bacterial killing occurred more rapidly under dry conditions than under moist ones (38, 41–43). Using a wet inoculum, bacteria such as *Enterococcus faecalis* or *Enterococcus faecium* were killed in 1 h, compared to 10 min when presenting the inocula to the metal coupons in lower volumes (20 μl) (27). Also, the effects of temperature (26, 34, 44) and relative humidity (26, 44–46) were explored.

Michels et al. conducted laboratory tests studying the effects of temperature and humidity on the biocidal efficacy of copper- and silver-containing materials on MRSA (26). They used the standard methodology of that time, JIS Z 2801, originally the Japanese Industrial Standard (JIS Z 2801), which utilizes temperatures approximating that of human skin (35°C) and high humidity (>90%) and compared it to situations with lower tempera-

tures (20°C) and lower humidity (20%). Under all test conditions, a >5-log reduction of CFU after 24 h was achieved on copper, although slight differences were seen when changing the temperature and humidity. Their results were a >6.4-log reduction of CFU at 35°C and >90% humidity on copper, which dropped slightly to a >6.1-log reduction when lowering the temperature to 20°C. Testing under lower humidity showed a larger difference: at 20% humidity and 35°C, there was a slightly lower reduction than that at >90% humidity (>5.5-log versus >6.4-log reduction, respectively). Interestingly, silver also demonstrated >6.4- and 5.5-log reductions at high humidity at 35°C and 20°C, respectively; however, this was quickly reduced to a <0.3-log reduction at 24% humidity and 20°C but no log reduction at 20% humidity and 35°C.

As a result of the substantial amount of evidence, copper is the only hard surface material that has been approved by the U.S. Environmental Protection Agency (EPA) to make public health claims under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), a federal law of the United States (47) that is responsible for the governance of pesticides to protect applicators, consumers, and the environment (48). Registered public health claims are as follows: antimicrobial copper alloys continuously reduce bacterial contamination, antimicrobial copper is able to kill >99.9% of bacteria within 2 h of contact, antimicrobial copper remains effective in killing >99.9% of bacteria after repeated recolonization, and antimicrobial copper inhibits bacterial growth between routine cleaning activities.

Apart from the horizontal transmission of pathogens through hard surfaces, studies are suggesting the potential hazard of soft surfaces in health care environments (white coats, privacy curtains, and bed linen, etc.) for cross-contamination (49–52). To address this issue, the introduction of copper into textiles and liquids was explored. Due to recent developments in nanotechnology, it has been made possible to impregnate textiles, latex, and other polymer products with copper oxide (13). Metal nanoparticles are particularly interesting because of their enhanced antimicrobial ability compared to hard surfaces and the possibility of embedding them into polymer structures. Their enhanced antimicrobial ability is explained by their high surface area compared to their volume; therefore, cell membranes are more rapidly penetrated (53, 54). Laboratory studies have provided solid evidence of the broad-spectrum antimicrobial properties of copper-impregnated fibers of which socks, face masks, filters, bed linen, and scrubs, etc. can be made (8, 13, 28, 55–61) (Table 1). A research team in Israel was the first to report on copper-impregnated products and their antimicrobial properties (13). Cotton fibers and latex were impregnated with copper ions, and their effectiveness against bacteria (E. coli, S. aureus, MRSA, and VRE), fungi (Candida albicans), and viruses (HIV-1$_{IIIB}$ and West Nile virus) was compared to that of a noncopper equivalent. A >2-log reduction of all four bacteria was demonstrated within 2 h of exposure to copper fabrics. The copper fabric was also able to completely inactivate fungi in 60 min of exposure, and copper-impregnated latex gloves were able to reduce the infectivity of both viruses. The same team also conducted animal studies and demonstrated that copper-impregnated fabrics did not possess skin-sensitizing properties. Since then, more studies have been conducted, especially on copper impregnated fabrics. In 2006, the same research team reported results of biocidal studies of different copper oxide-impregnated fabrics (cotton, polyester, polypropylene, and nylon) against a wide variety of bacteria, fungi, and viruses (55), again showing that copper fabrics reduced the numbers of viable bacteria, fungi, and viruses by >98.7% within 20 min to 4 h of exposure.

Mechanism of Action

The mechanism by which copper kills microorganisms is multifaceted and not yet fully understood. Literature suggests that copper interacts with microorganisms on different cellular levels, all resulting in cell death, including cell membrane permeabilization, membrane lipid peroxidation, protein alteration, and denaturation of nucleic acids.

Copper ions released from the surface are transported through the cell membrane via an energy-dependent transport system. A decreased barrier function of the plasma membrane occurs upon reaching a crucial intracellular concentration of copper ions.

The membrane becomes increasingly permeable, leading to leakage of vital cell content such as nucleotides, amino acids, and potassium (62, 63); Warnes et al. (64) demonstrated rapid membrane depolarization and loss of membrane integrity upon exposure to metallic copper surfaces, leading to cytoplasmic accumulation of free radicals.

Another mechanism by which copper damages the cell membrane is via the formation of reactive oxygen species (ROS). Copper ions are able to donate and accept electrons and thereby can change between Cu^+ and Cu^{2+} via oxidation. This catalyzes the formation of ROS such as hydroxyl radicals (HO) and superoxide anions (O_2^-); causes oxidative stress to membrane lipids (lipid peroxidation), amino acids in proteins, and nucleic acids; and causes oxidative deactivation of enzymes (27, 63–69).

Essential metals are required for proper protein function through a process called coordination chemistry (70). They are needed as cofactors and to catalyze cytotoxic reactions. Proteins controlling the activity of intracellular metal ions include membrane transporters, metalloregulating proteins, and metallochaperoning proteins. Metal ions are able to bind to certain atoms of protein complexes, such as oxygen (O), nitrogen (N), and sulfur (S) (71). Proteins exert preferences for binding specific metal ions because of their atomic structure (72). However, when metal homeostasis is distorted, metal ions such as Cu^{2+} are able to compete with other essential metals, for instance, iron ions (Fe^{2+}), and prevent proteins from binding with the correct cofactor and consequently inhibiting protein function (63). For instance, the protease of HIV-1 is inhibited by the binding of copper ions to the amino acid cysteine (73). Another example is the inactivation of protein tyrosine phosphatases through the oxidation of cysteine residues on the phosphatases by copper ions (74). Furthermore, the enzyme isopropylmalate dehydratase in *E. coli* is inactivated by displacing iron atoms by copper ions from the iron-sulfur clusters within the enzyme, a process called mismetallation (75).

Antimicrobial Resistance

Bacterial resistance to antibiotics, which has emerged in less than 50 years since the widespread use of antibiotics, is a major concern. However, only very recently has evidence of copper resistance been demonstrated despite its use over thousands of years (76). More frequently, a reduced sensitivity to copper has been observed but not at the exposure levels present in products used to control the concentration of microbes in the built environment. Bacteria which have been exposed to low concentrations of copper for a long period of time demonstrate increased tolerance to copper through the development of efflux pumps for active excretion of excess copper (77), impermeability to copper by membrane alterations (78), intra- and extracellular binding of copper (78–81), and detoxification of copper by enzymes (82). Despite these mechanisms, continuous exposure to high concentrations of copper is fatal for copper-tolerant microorganisms (83, 84). The rapid and multifactorial mechanism of action, which includes denaturation of DNA, makes it highly unlikely that microorganisms will develop resistance to copper. However, exposure to copper may upregulate nonspecific antibiotic resistance mechanisms, such as reduced membrane permeability, antibiotic alteration, efflux pumps for antibiotics, alteration of cellular targets, and antibiotic sequestration, which eventually could lead to increased antibiotic resistance (85).

ANTIMICROBIAL ACTIVITY OF COPPER IN A CLINICAL SETTING

There is ample evidence to support an important role of the surface contamination of the environment in the spread of HAIs (86). Research into the survival of nosocomial pathogens on surfaces has demonstrated that many pathogens, such as MRSA, VRE, *Acinetobacter* spp., *Pseudomonas* spp., and norovirus, are able to survive days to weeks on environmental surfaces, with a survival of months for *Clostridium difficile* (87, 88). Surface contamination with MRSA or VRE has been documented for up to 60 to 70% of hospital surfaces (89, 90). Hand contamination is a well-known vector of spreading pathogens, particularly through health workers (91). The bacterial burden, which can be expressed by positive environmental surface cultures, is the most important risk factor for hand contamination (92). Clinical research has shown that fewer than half of the

hospital touch surfaces are clean due to inadequate disinfection (93, 94). Apart from techniques such as cleaning and disinfection to decrease the transmission of pathogens (95, 96), self-disinfecting touch surfaces have been developed (97).

Copper as an Antimicrobial Hard Surface

Copper was first clinically investigated as a biocidal surface material. The first clinical article was written in 1983 by an American physician from Philadelphia, PA, Phyllis J. Kuhn (98). She involved domestic staff from the local hospital in a small study to increase their awareness of modes of infection. They were given culture plates with instructions to return them with cultures from different sites in the hospital. The test showed that a brass doorknob (67% copper and 33% zinc) had very few bacterial colonies, in contrast to stainless steel doorknobs, with heavy growths of both Gram-positive and Gram-negative bacteria. Repeated experiments using a high inoculum of *E. coli*, *S. aureus*, group D *Streptococcus*, and *Pseudomonas* sp. showed rapid disinfection on brass and copper, compared to heavy growths on stainless steel and aluminum.

Since then, a number of clinical studies have been carried out in different parts of the world, serving to lend clinical relevance to incorporating copper surfaces into the built environment in order to reduce the resident microbial burden and thereby reduce the risk of infection (the United Kingdom [99–101], Germany [102], the United States [12, 103–105], Chile [106], and South Africa [40]). Work done in a university hospital in Birmingham, United Kingdom, replaced three items in an acute medical ward using copper facsimiles for the toilet seat, tap handles, and door push plates for a period of 10 weeks. Here it was observed that when the ward was sampled for the presence of microorganisms, the copper facsimiles harbored 90% fewer microbes (median values) than the original objects to no microbes at all that could be retrieved (99). This study was further extended by replacing 14 frequently touched items (trolleys, light pulls, flush handles, overbed tables, dressing trolleys, and commode chairs) for copper-containing items on the same medical ward. Again, these items were compared to noncopper equivalents over a period of 24 weeks. This study showed that all 14 items had a reduced bacterial load and that 8 of the 14 items demonstrated a significant reduction compared to noncopper items. Furthermore, antibiotic-resistant bacteria were significantly less frequently cultured on copper items (101).

Research conducted in other parts of the world showed similar results. For example, a study in a South African primary health care clinic showed a 71% reduction of CFU on copper surfaces (40). A study on an oncology/pneumatology and geriatric ward in Germany showed a CFU reduction of 30% on copper and a significantly delayed repopulation compared to standard items (102). In Chile, copper surfaces were installed in 3 rooms on an intensive care unit (ICU) and compared with 3 control rooms. The mean microbial burden was significantly reduced by 49 to 93% in the copper-containing rooms (106).

The U.S. army funded a large-scale, multicenter, randomized, controlled trial with the aim to assess the antimicrobial properties of copper surfaces in ICUs. Eight ICU rooms in three different hospitals had the most contaminated surfaces replaced with copper and were matched with control rooms. The average microbial burden was 83% lower on copper surfaces than on noncopper surfaces (103). In 2011, Casey et al. studied the contamination of copper and stainless steel pens used in the hospital (100). Fifty copper pens (85% copper and 15% zinc) and 50 stainless steel pens (100% stainless steel) were disinfected and distributed to nurses on two critical care units. After being used for one 12.5-h shift, half of the pens (25 copper and 25 stainless steel pens) were immediately sent to the laboratory for microbial sampling, and the remaining 50 pens were stored for 11 h at room temperature before being sent to the laboratory. They found that upon immediate sampling, there was a nonsignificantly lower number of contaminated copper pens than stainless steel pens (48% and 68%, respectively). After storing the pens for 11 h, a significantly lower number of contaminated copper pens was found (20% versus 72%; $P = 0.0005$). Likewise, a significantly lower number of CFU was found on copper pens than on stainless steel pens upon

immediate testing (median [lower to upper quartiles] of 0 [0 to 4] versus 12 [0 to 20]; $P = 0.04$) and after 11 h of storage (median [lower to upper quartiles] of 0 [0 to 0] versus 8 [0 to 80]; $P = 0.0002$). More recently, the microbial burden of a standard stethoscope was compared to that of a similar one with 4 parts replaced with copper-containing parts (diaphragm, binaural tube, and the two ear tubes) (107). Different health care professionals (fellow and resident physicians and pediatric nurse practitioners) alternately used the control and copper stethoscopes for 1 week on four separate occasions. They found significantly lower concentrations of bacteria on copper stethoscopes than on the control ones (11.7 versus 127.1 CFU; $P < 0.00001$). Salgado et al. (12) were the first to report a study on the effect of copper surfaces on the incidence of HAIs. During the study period of almost 1 year, patients were randomly placed into rooms with or without copper touch surfaces. The incidence of HAI and/or MRSA or VRE colonization in ICU rooms with copper showed a significant reduction of 42%, and the incidence of HAI alone was 58% lower in copper rooms than in the control rooms (12).

All the studies mentioned above provide substantial evidence of the antimicrobial and infection prevention abilities of copper surfaces in clinical settings.

Antimicrobial Copper-Impregnated Soft Surfaces

Studies in a clinical setting have been performed only more recently. Gabbay et al. reported the first study using copper oxide-impregnated socks and sheets (55). The copper-impregnated sheets were tested in a clinical setting on a general internal medicine hospital ward, where 30 patients slept overnight on regular sheets and copper-impregnated sheets were used the following night. They reported that bacterial colonization was significantly lower on copper sheets than on regular sheets. A study population of 100 individuals with tinea pedis were asked to wear copper oxide-impregnated socks on a daily basis and to stop antifungal treatment. All 100 individuals reported a complete relief of symptoms of burning and itching within 1 to 3 days of wearing the socks. The skin affected by tinea pedis significantly improved within a week. Subsequently, the same team in Israel conducted another study on copper oxide-impregnated socks (108). Fifty-six patients with severe tinea pedis were asked to wear normal socks for the first week and continue wearing copper socks from the second week onwards in the absence of any other treatment. Follow-up results after averages of 9 days and 40 days showed either improvement or resolution of symptoms of tinea pedis (erythema, fissuring, vesicular eruptions, scaling, and burning and itching) for the whole cohort. No adverse reactions to the copper-impregnated socks were identified (108). These results were then confirmed in a study using photographs taken in the previous study and quantitatively measuring them with a computer program (109). An unplanned study was carried out in 2010 when 33 miners were trapped for 69 days in a mine in Chile (110). The miners suffered from severe fungal skin problems, mainly of their feet. An antifungal cream was delivered to the trapped miners, but the cream application was unsuccessful. Therefore, after more than a month, copper oxide-impregnated socks were delivered, and this proved to be effective. After rescue, it was noted that the miners' skin condition was exceptionally good given the circumstances in which they were trapped. In 2013, a study on the use of copper oxide-impregnated socks for the protection of soldiers' feet was published (111). Fifty-three soldiers filled out a questionnaire after wearing the socks for 3 weeks during intensive basic training. The majority reported a significant reduction of skin irritation, itching, and dryness of their feet and reduction of foot and sock odor.

More recently, the effect of copper-impregnated textiles on HAIs has been studied in two clinical trials (112, 113). The first trial compared the HAI rates on a specialized ward for patients with head injuries over 1 year, separated into two time periods: one period prior to the replacement of bed linens and uniforms worn by staff with copper-impregnated textiles and the second period after substitution of the hospital textiles (112). Replacing regular textiles with copper-impregnated textiles resulted in a significant reduction of 24% in the HAI rate. Furthermore, significant reductions were observed in the number of fever days (reduction of 47%) and in the total number of

days of antibiotic treatment (32.8% reduction), and a savings of 27% in hospital costs was accomplished. A second study conducted on two ventilator-dependent wards showed similar results for HAI indicators in a crossover, double-blind, controlled trial (113). Copper fabrics (bed linen, clothing, and towels for patients) were given to one ward, and nonimpregnated textiles were given to the other ward, for a period of 3 months. After a 1-month washout period with the hospital's usual textiles, copper and control textiles were exchanged for another 3 months. All staff were blind to the nature of the fabrics. Significant reductions were observed in all four indicators for infection, namely, the need for antibiotic treatment (29.3% reduction), number of days with a fever (55.5% reduction), duration of antibiotic therapy (23.0% reduction), and daily dose of antibiotics used (27.5% reduction). Adverse events or skin irritation was not reported.

These trials suggest a positive effect of the use of copper-impregnated textiles to augment infection control practices in a health care environment. Additional and more robust trials (e.g., randomized, blind trials) are required to learn the complete benefit that copper textiles offer in lowering the risk of HAI.

WOUND HEALING

Wound healing is a complex cascade of events on a cellular level which comprises four stages: hemostasis, inflammation, proliferation, and remodeling (114) (Fig. 4). Hemostasis is dominated by platelets, which release two main factors: platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β). Inflammatory cells such as neutrophils, mast cells, macrophages, and T lymphocytes clean the wound from injured and contaminated tissue in the inflammatory phase. Characteristic features of the proliferation phase epithelialization, fibroplasia, and angiogenesis. Epithelialization is stimulated by epidermal growth factor (EGF) and TGF-α, which are produced by macrophages. Angiogenesis is initiated by vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (bFGF), and TGF-β. During remodeling, matrix proteins such as collagen, proteoglycans, and fibronectin are produced and form tight connections to increase the strength of the scar.

Dysregulation of this complex mechanism will result in fibrosis and chronic ulceration and is associated with increased morbidity and mortality (115–118). According to the literature, the function of many factors involved in wound healing is dependent on and modulated by copper ions, and thus, copper is involved in all four stages of wound healing (74, 119–132). It is hypothesized that delayed wound healing could partially be explained by depleted copper levels (10), which in turn reinforces a role for this element as an essential micro-trace nutrient required from diet.

Effect of Copper on Hemostasis and the Inflammatory Response

PDGF plays a significant role not only during hemostasis but also during the several stages of wound repair. It stimulates not only the proliferation and migration of fibroblasts and smooth muscle cells but also the migration of inflammatory cells such as neutrophils and macrophages (133). *In vitro* studies have provided insight that the cell migration stimulated by PDGF is copper dependent (130) and that copper plays an important role in the first two stages of wound healing. Copper accumulates during the inflammation phase, where it will be used by inflammatory cells such as macrophages (134, 135).

Effect of Copper on Proliferation

Copper's role in facilitating angiogenesis has been known for some time (136–138), but only more recent studies have shed light on the specific copper targets. VEGF is an important growth factor which stimulates angiogenesis, a key part of the proliferation phase. Copper is able to induce VEGF expression in keratinocytes, which is confirmed by enhanced VEGF expression in copper-treated wounds (125). Furthermore, the release of two polypeptides also involved in angiogenesis, fibroblast growth factor 1 (FGF-1) and interleukin 1α (IL-1α), is upregulated by copper (139).

Bleeding

Blood clot

Epidermis

Dermis

Red blood cells

Subcutaneous fat

Blood vessel

Inflammatory

Macrophage

Fibroblast

Proliferative

Fibroblasts
proliferating

Remodeling
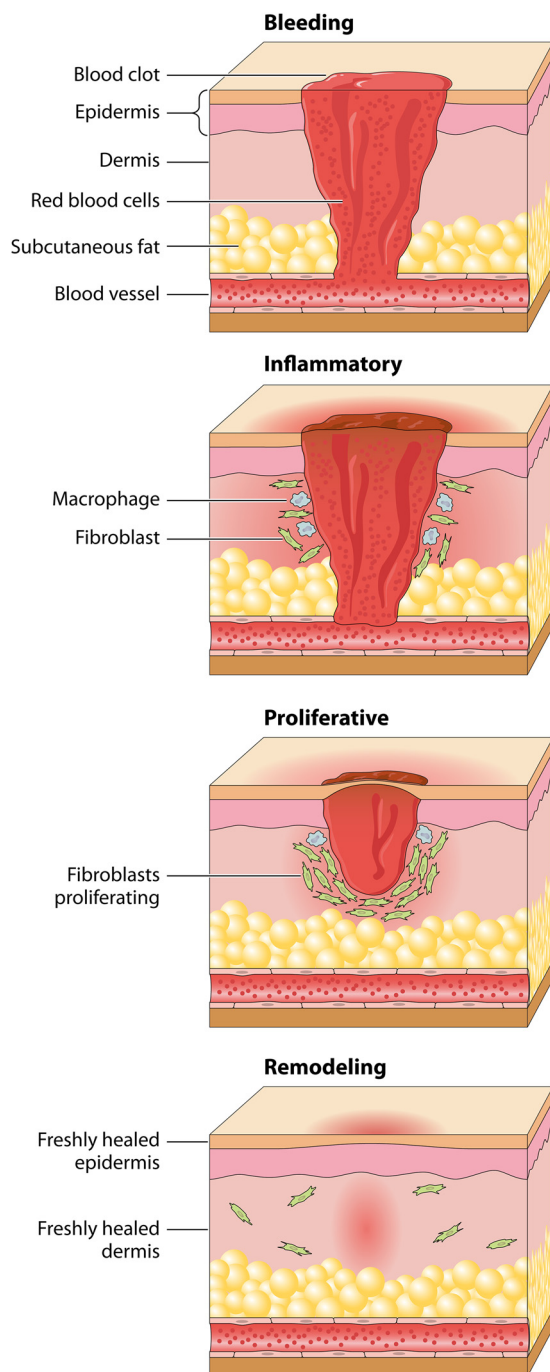
Freshly healed
epidermis

Freshly healed
dermis

FIG 4 Mechanism of wound healing. Wound healing is a complex cascade characterized by four overlapping phases: bleeding and hemostasis, inflammation, proliferation, and remodeling. At the time of injury, the tissue is disrupted, and the platelets stick together to seal damage to the blood vessel. After this, fibrin strands begin to adhere. Following hemostasis, the neutrophils enter the wound site and begin removing foreign materials, bacteria, and damaged tissue. The inflammatory phase continues with highly phagocytic macrophages that are responsible for removing nonfunctional host cells, bacterium-filled neutrophils, damaged matrix, foreign debris, and any remaining bacteria. Once the wound site is cleaned out, the migrated fibroblasts begin the proliferation phase. The objective of the proliferation phase is for the wound to be "rebuilt" with new granulation tissue, which is comprised of collagen and extracellular matrix and into which a new network of blood vessels develops, a process known as angiogenesis. Epithelial cells finally resurface the wound, a process known as epithelization. During the final remodeling phase, the collagen forms well-organized stable cross-links.

Effect of Copper on Remodeling

During remodeling, fibronectin mats are formed to strengthen the scar. Fibronectin stabilization and cell ingrowth are stimulated by low concentrations of copper (140). Copper also forms complexes with the tripeptide glycyl-L-histidyl-L-lysine (GHK), which upregulate important remodeling proteins such as collagen, elastin, metalloproteinases, VEGF, fibroblast growth factor, and nerve growth factor (141, 142). Furthermore, cross-linking of collagen and elastin is catalyzed by the copper-dependent enzyme lysyl oxidase (LOX) (143).

Copper-Impregnated Products for Antiaging Skin Therapy and Improvement of Skin Pathologies

The positive effect of copper oxide-impregnated products on the skin was also demonstrated in two double-blind randomized trials using copper-impregnated pillowcases. Borkow et al. reported a double-blind, placebo-controlled, randomized study (144). Fifty-seven volunteers aged 40 to 60 years slept on either a copper oxide-impregnated or a control pillowcase during the study period of 4 weeks. Facial photographs at baseline and after 2 and 4 weeks were evaluated by a dermatologist and a cosmetologist. Sleeping on a copper oxide-impregnated pillowcase resulted in a significant reduction of wrinkles and crow's-feet and resulted in an overall improved facial appearance at both 2 and 4 weeks compared to sleeping on a normal pillowcase. A similar study was conducted by Baek et al. (145), although a longer study period was chosen (8 weeks), and facial photographs were also evaluated by GFM PRIMOS three-dimensional (3D) image analysis at baseline and at 4 and 8 weeks. Results from 61 volunteers using either a copper oxide-impregnated or control pillowcase showed a significant decrease of crow's-feet in the copper group and no decrease in the control group. The 3D analysis revealed a decrease of facial wrinkles in the copper group but failed to detect changes in the control group. These results were substantiated by Dykes (146), who studied the effect of copper oxide-impregnated socks on skin elasticity. In a double-blind, placebo-controlled study involving 60 healthy volunteers in which about half of the group wore copper oxide-impregnated socks and the other half wore identical socks without copper for 4 weeks, skin elasticity on the side of the ankle was measured at baseline and after 2 and 4 weeks using a cutometer. The results showed an increase of mean net skin elasticity of 6.4% at 2 weeks and a significant increase of 31.4% at 4 weeks in the group using copper socks but no increase in elasticity in the control group. In a preliminary clinical study regarding the safety of adult diapers impregnated with copper oxide in elderly patients, an improvement of skin appearance was found (147). Sixteen patients used the copper diapers daily for a period of half a year. During the study period, no skin irritation or adverse reactions related to the diapers were observed. After 1 month of usage, an improved skin appearance in the diaper area was observed in all participants. Arendsen et al. studied the effect of copper-impregnated compression stockings on the skin condition lipodermatosclerosis secondary to chronic venous insufficiency (148). In a double-blind, randomized, controlled study, they included patients with bilateral lipodermatosclerosis. The participants were given pairs of study compression stockings, of which one of the pairs was impregnated with copper and the other was a control stocking. This study demonstrated a significant reduction of lipodermatosclerosis using copper-impregnated stockings.

SAFETY OF COPPER

Copper is one of a few metallic minerals which are essential for normal functions of several processes in the human body. It is estimated that humans digest about 1 mg of copper per kg of body weight daily (149). Depending on the copper content and form of copper, 15 to 97% of the copper is absorbed in the stomach and small intestine (150–153). Various copper transporters move the ingested copper through cell membranes (154, 155), after which copper binds to albumin, glutathione, and amino acids (156, 157). The primary site of copper uptake is the liver, where it is incorporated into

copper-dependent proteins. The liver controls copper release and thereby maintains copper homeostasis (158). Copper is excreted through feces, and the majority of fecal copper comes from biliary excretion (159–161). The human body utilizes copper for the innate immune response by increasing the phagocytic and bactericidal activities of neutrophils and the antimicrobial function of macrophages (162). Signs and symptoms of copper deficiency include anemia, neutropenia, myelopathy, and peripheral and optic neuropathy (163–165). Copper toxicity due to excess ingestion of copper is rare; however, it can lead to nausea, vomiting, hematemesis, hypotension, melena, jaundice, and diarrhea (166). Chronic copper excess can damage the liver and kidneys (167). High internal copper concentrations can result from a genetic disorder, Wilson's disease is a rare autosomal recessive disease affecting between 1 in 30,000 and 1 in 100,000 of the population. Wilson's disease affects the proper metabolism of copper and is associated with a reduced rate of copper excretion through bile, resulting in a toxic accumulation of the element within the liver (168). Clinical manifestations include hepatic (elevated serum aminotransferase levels, chronic hepatitis, cirrhosis, and hepatic failure), neuro-logical (tremor, choreiform movements, Parkinsonism, gait disturbances, dysarthria, seizures, and migraine), ophthalmic (K-F rings and sunflower cataracts), psychiatric (depression, neuroses, and psychosis), and renal abnormalities.

Even though a high internal concentration of copper is toxic, the exogenous application of copper is considered safe to humans. Such a claim is supported by the fact that, for almost 50 years, copper intrauterine devices (IUDs) have been safely used for up to 10 years of single placements, with no reported adverse effects (169). Globally, copper pipes are widely used for the distribution of water because of their ability to resist corrosion. Copper is also safely used in health care for the control of *Legionella* (170) and other waterborne bacteria (171) through a copper-silver ionization water filter, in dentistry for the reduction of carries (172) by using high copper concentrations in dental amalgam alloys, and for the prevention of foodborne diseases (23, 34, 173) on copper alloy surfaces. Furthermore, the use of copper as a biocide has become indispensable and is frequently used in antifouling paints (174, 175); for wood preservation (176); for the control of green algae in lakes, rice fields, canals, rivers, and swimming pools (90); and for the prevention of the fungal disease of grapes (downy mildew) (177).

The safety of copper-impregnated textiles is studied through extensive animal studies, which all demonstrate no skin irritation or sensitization or any other adverse reaction to copper oxide-impregnated textiles (13, 28, 55, 61). Subsequently, its safety in humans was demonstrated in various clinical trials (108, 110, 144, 145, 178). Contrary to microbes, human skin cells are able to metabolize and utilize copper, and conse-quently, the risk of adverse reactions is negligible (179). In contrast to human cells, microorganisms are exceedingly sensitive to excess concentrations of copper, as they cannot control their extracellular environment to allow for excretion (75). Other metals commonly used in health care, such as aluminum, nickel, and silver, cause harm to the environment, and even though human cells are also able to utilize aluminum and other trace metals, significant health issues have been documented. Apart from the obvious adverse effects on the respiratory tract for aluminum industry employees, aluminum drinking levels in potable water are also positively associated with the risk of cognitive impairment, dementia, or Alzheimer's disease (180). The use of nickel-containing products is increasing, which led to an increased environmental burden of nickel compounds, a serious health risk for humans, as nickel is not an essential element for humans. Nickel can result in skin sensitization, lung fibrosis, poisoning of the kidneys and the cardiovascular system, and tumor formation (181).

Silver is applied in hygiene, personal care, and health care as silver coatings on hard surfaces, spray for prevention of sore throats, and silver-impregnated dressings for treatment of chronic wounds (182). The production and usage of silver nanoparticles pose a threat for the environment and humans. Environmental toxicity is caused by soluble free silver ions that are released from industrial wastes. Adverse effects on humans include permanent discoloration of the skin (argyria) or the eyes (argyrosis); liver and kidney damage; irritations of the eyes, skin, respiratory system, and intestinal

tract; and strong toxic effects on the proliferation of and cytokine expression by peripheral blood mononuclear cells (183). As silver ions are soluble, silver-impregnated products will leach silver ions during washing or recycling. In contrast, copper oxide is nonsoluble, and copper oxide-impregnated products will therefore not pollute the environment and, as such, will have permanent antimicrobial properties.

CLINICAL APPLICATION IN OBSTETRICS AND GYNECOLOGY

To date, there is little to no research on copper specifically in the field of obstetrics and gynecology, although the clinical application of copper can be extrapolated from current evidence. However, infection prevention practices can be very challenging. The "normal" microflora of the vagina and cervix can, under certain circumstances, lead to infection of the female genital tract, and these infections are usually polymicrobial (14). Particularly in obstetric practices, there is a higher risk of transmission of infectious diseases due to frequent contact with blood and other bodily fluids. During the 19th century, Ignaz Semmelweis discovered that puerperal fever was transmitted from the morgue to laboring women via the hands of medical students. Due to his introduction of antiseptic procedures, the mortality rate from puerperal fever dropped to below 1% (184). HAIs are a global problem associated with a significant impact on morbidity and mortality. Plowman et al. reported an overall incidence of HAI of 7.8%, which varied considerably with specialty, with the highest incidence of 13.1% in gynecology and the third highest incidence of 10.1% in obstetrics (185). Johnson et al. have shown that 10% of women undergoing vaginal delivery who sustained perineal trauma that required suturing developed a wound infection (186).

Surgical site infections (SSIs) are one of the most prevalent reported nosocomial infections. They account for 14 to 16% of all hospital-acquired infections. With cesarean section (CS) rates rising (187–190), the risk of surgical site infections is also subject to an increased frequency despite the use of prophylactic antibiotics, with the rate ranging between 2% and 15% (191–197). MRSA has caused a larger number of severe postpartum infections, especially after CS (198–200). Approximately 10% of asymptomatic pregnant women are colonized with MRSA (201, 202). Reduction of the microbial burden in the vicinity of a surgical wound may limit surgical site infections or at least simply reduce the incident risk following not only CS but also other gynecological (abdominal) surgeries. Recently, the results of the first clinical trial studying the effect of copper-impregnated wound dressings on SSI rates following CS were presented by Arendsen et al. at the European Congress of the European Board and College of Obstetrics and Gynaecology (203). This comprehensive, single-center, double-blind, randomized, controlled trial included 324 participants, of whom 156 were randomized to the copper-impregnated dressing group (study group) and 159 were randomized to the noncopper wound dressing group (control group). All women following cesarean section, both planned and emergency, were eligible for study enrollment. The primary study outcome was the incidence of SSI within a 30-day period following CS. The Health Protection Agency's Post Discharge Questionnaire for national (United Kingdom) SSI surveillance was used for the assessment of SSI (204), which is in keeping with the worldwide-used definition of SSI by the Centers for Disease Control and Prevention (205). With a follow-up rate of 100%, there was a significant 38% lower overall SSI rate in the copper intervention arm than in the control group (adjusted odds ratio [OR], 0.44 [95% confidence interval {CI}, 0.25 to 0.77]; $P = 0.004$).

Vaginal trauma from vaginal surgery or delivery can also lead to wound infection. The prevalence of vaginal lacerations following vaginal delivery is as high as 85%, and up to 70% will need suturing (206). Because of factors supporting the development of inflammation, such as higher local humidity and the presence of various microbes, obstetric trauma has a high risk of wound infections of 11% (186). Wound infections can cause wound breakdown associated with pain, resulting in a delay in healing, and this can have a negative impact on motherhood (207). Furthermore, antibiotics are able to pass into breast milk and can disrupt the microbiome of the developing infant gut. One of the leading causes of maternal mortality worldwide is bacterial infections resulting

from delivery and during the postpartum period. These infections account for 11% of the global burden of maternal deaths (16, 208). The use of copper-impregnated sanitary pads may help limit (wound) infections after vaginal surgery or vaginal delivery. As endometritis is often caused by an ascending infection from the lower genital tract, it was hypothesized that using sanitary pads impregnated with copper in the time immediately postpartum may be able to limit this serious maternal complication. The results of the first trial studying copper-impregnated sanitary towels was recently presented by Arendsen et al. at the European Congress of the European Board and College of Obstetrics and Gynaecology (209). This double-blind, randomized, controlled trial included 450 women who sustained a secondary tear or episiotomy during a vaginal delivery. Half of the study population used copper-impregnated maternity pads. The study demonstrated a significant reduction of the overall infection rate in the copper group by 78%.

Copper-impregnated sanitary pads or tampons could also be effective for the treatment of vaginitis. Vaginal microbiota dominated by the anaerobic *Lactobacillus* are a well-known marker of healthy vaginal flora (210). *Lactobacillus* is able to inhibit the growth of pathogenic microorganisms such as *Bacteroides fragilis*, *E. coli*, *Gardnerella vaginalis*, *Mobiluncus* spp., *Neisseria gonorrhoeae*, *Peptostreptococcus anaerobius*, *Prevotella bivia*, and *S. aureus* (211–214). *Lactobacillus* spp. generate a low pH, resulting in a vaginal pH of less than 4.5 (215). Additionally, *Lactobacillus* spp. generate hydrogen peroxide, a significant inhibitor of anaerobes and facultative anaerobic bacteria lacking or possessing reduced levels of catalase (216, 217). Studies suggest that the biocidal ability of copper is enhanced by the conversion of hydrogen peroxide to hydroxyl radicals (ROS) catalyzed by copper, and copper is a more efficient catalyst ($\sim$100-fold) than Fe^{2+} in catalyzing the Fenton reaction, which generates significant hydrogen peroxide (218). A distorted balance of the vaginal microbiota can lead to an overgrowth of anaerobic microbes (bacterial vaginosis); facultative anaerobic species such as *E. coli*, enterococci, and group B streptococci (aerobic vaginitis); or both. A healthy, acidic vaginal microflora is especially important during pregnancy, as studies have suggested that vaginal infection is an important risk factor for complications of pregnancy. For instance, premature births and spontaneous abortions have been associated with bacterial vaginosis, which occurs in up to 20% of pregnant women (219). No research has been done to establish the effect of copper on *Lactobacillus* spp.; however, given the fact that the generation of ROS is part of the antimicrobial efficacy of copper as well as *Lactobacillus* spp., it can be hypothesized that these bacteria could be less sensitive to copper. It is expected that during continued exposure to copper, members of the healthy vaginal microflora such as *Lactobacillus* would eventually be harmed. In contrast to antibiotics, which will kill only a specific spectrum of bacteria, leaving other bacteria or microbes to flourish, copper is able to kill all microbes, preventing an overgrowth of a particular microorganism. Local application of copper-impregnated products such as underpants, sanitary/maternity pads, and tampons could help in the treatment of vaginitis and might also have the ability to prevent complications related to vaginitis in pregnancy.

Copper IUDs have been safely used for almost 50 years, with up to 10-year single placements without any adverse effects (169). A common concern among health care providers is whether the insertion of an IUD increases the risk of lower and upper genital tract infections, which can lead to pelvic inflammatory disease (PID), with its associated risk of infertility. This is particularly important since the majority of IUD users are young women who are at a higher risk of sexually transmitted infections (STIs) (220). However, extensive research shows that the risk of PID was not increased with the use of an IUD (both copper- and levonorgestrel-containing IUDs) compared to other contraceptive methods, and there was no association with infertility (221–226). A case-control study assessing the association between the use of a copper-containing IUD and the level of antichlamydial antibodies even found evidence of a possible protective effect against chlamydia infection (227). Compared to women with an inert

IUD (not containing a bioactive component), women with a copper-containing IUD had significantly lower levels of antichlamydial antibodies.

In recent years, more attention has been given to the prevention of human papillomavirus (HPV) to reduce the mortality and morbidity of cervical cancer (228). Lekovich et al. studied the differences in clearance of HPV in women using copper-containing and levonorgestrel-containing IUDs (229). In this retrospective study, the cervical cytology of 150 women using a copper IUD was compared with the cervical cytology of 152 women using the levonorgestrel IUD, both before and after placement of the IUD. The results showed that a significantly lower proportion of the women using the levonorgestrel IUD cleared HPV infection than women using the copper IUD (42% versus 70%; $P = 0.04$). Furthermore, women using the levonorgestrel IUD had a 4-times-higher risk of acquiring a new HPV infection. It is still debatable whether this study shows a positive effect of the copper IUD on HPV clearance, a negative effect of the levonorgestrel IUD, or maybe a combination of the two. Spontaneous clearance of HPV has been documented in the literature to occur in 61% of women within 1 year (230). A higher rate of clearance was found in this study, although this was not statistically significant. The HPV clearance rate in women with a levonorgestrel IUD was found to be significantly lower than the spontaneous clearance rate ($P = 0.03$). Another study evaluated the association between recent IUD use and cervical intraepithelial neoplasia grade 2 (CIN2) and CIN3, adenocarcinoma, or cancer and found an increased risk of CIN grade 2 and higher (relative risk [RR], 1.18 [95% CI, 1.08 to 1.30]; $P < 0.001$) associated with the use of a levonorgestrel-containing IUD (231). Copper IUDs showed no association with precancer or cancer; a possible trend of a lower risk of CIN3$^+$ (RR, 0.81 [95% CI, 0.64 to 1.02]; $P = 0.07$) was found with the use of a copper IUD. Unfortunately, the group of women with a copper IUD was almost four times smaller than the levonorgestrel-containing IUD group, which could explain why statistical significance could not have been reached.

Twenty-five percent of all hospitalized patients have a urinary catheter (232), and nosocomial urinary tract infection (UTI) associated with urinary catheters accounts for 80% of all nosocomial infections (233). Symptoms of urinary incontinence are highly prevalent in both sexes; however, they are much more frequent in women. In the United Kingdom, as many as 50% of women suffer from urinary incontinence (234); therefore, urinary incontinence is a common problem seen in gynecological outpatient departments. Women suffering from severe urinary incontinence often end up with long-term catheterization (235). For this reason, research has been undertaken to investigate antimicrobial coatings for urinary catheters (236). Currently, silver is one of the few ingredients for medical products, such as coatings for urinary catheters, that is approved by the FDA. Extensive research has been carried out suggesting the antimicrobial ability of silver cations (237–243). The data concerning the overall effectiveness of silver cation-releasing catheters for their ability to prevent catheter-mediated UTI are limited (244–249). No studies to date have been done looking at the possibility of the use of copper-impregnated urinary catheters; however, there has been research done with copper-impregnated silicone in a different field of medicine. Gosau et al. investigated the antibacterial ability of copper-impregnated silicone for use in breast implants (250, 251). Their research showed reduced adherence of bacteria and bactericidal abilities of the copper-impregnated silicone.

Another possibility to reduce UTIs, especially in the elderly, is copper oxide-impregnated incontinence pads. The reported association of urinary incontinence and UTIs in the literature has been suggested to be caused by the transmission of bacteria during daily incontinence care (252, 253) and through the use of incontinence pads (254). Omli et al. demonstrated an almost 4-times-increased risk of UTI with the use of incontinence pads (255). Weinberg et al. studied copper oxide-impregnated incontinence diapers for chronic care patients (147). The frequencies of infections that occurred over the study period were similar to, if not slightly lower than, those for the same period a year before. Unfortunately, this study was not designed to detect a significant difference in infection rates.

CONCLUSION

Although there is considerable *in vitro* research supporting the antimicrobial properties of copper, there is still a paucity of *in vivo* studies. With the advancement of research toward clinical studies, the antimicrobial application of copper in health care is becoming more evident. The continuous and rapid broad-spectrum biocidal properties of both copper-containing hard surfaces and soft surfaces such as textiles and polymers may offer a novel and innovative advancement in the battle against health care-associated infections. Although traditional infection prevention practices should not be abandoned, copper-coated surfaces and textiles could increase their effectiveness. This review has provided an overview of the current evidence of the antimicrobial and wound-healing properties of copper and explored its potential uses in obstetrics and gynecology. Although some studies provide evidence for clinical applications of copper in a health care setting, more robust clinical, randomized, controlled research is needed to further confirm the use of various copper-impregnated (medical) products for the prevention of infection. Within obstetrics and gynecology, copper-impregnated products may be useful for infection prevention, e.g., copper-impregnated wound dressings for the prevention of surgical site infection following cesarean section and other abdominal gynecological surgeries; copper-impregnated incontinence pads for the prevention of wound infection after perineal suturing (following vaginal delivery or vaginal surgery), for the prevention of UTIs associated with the use of incontinence pads, and for the treatment of vaginitis; copper-containing IUDs, which may have a protective ability against chlamydia and HPV infection; and copper-impregnated urinary catheters for the prevention of UTIs associated with long-term catheterization. As sepsis is one of the major causes of maternal mortality, the introduction of copper-impregnated materials in the health care setting could have a dramatic impact on the reduction of infections. Given the emerging and constant resistance to antibiotics, copper provides a nonpharmacological alternative in terms of both prevention and treatment of infections. The impact of these benefits is likely to be greater in low-resource countries where access to medicine, especially antibiotics, is limited.

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